REMARKS

Currently, claims 28, 30-31, 33-35, 37-38, 40, 42-44, 46, and 62-67 including independent claim 28, are pending in the present application. Claims 66 and 67 have been withdrawn as there is presently no allowable generic claim. Independent claim 28, for instance, is directed to a method of utilizing a triggerably releasable delivery system. The method comprises administering to a mucosal membrane of a patient a plurality of nanoparticles containing silica coated with alumina and having a size of about 500 nanometers or less. The alumina provides a site on a surface of the nanoparticles to which is bonded a functional compound. The nanoparticles also possess a positive surface charge, i.e., a zeta potential of about 20 millivolts or more. The nanoparticles are contained within a vehicle that further comprises a pH altering material (e.g., acid or base). The functional compound is released from the surface of the nanoparticles upon exposure to a change in pH.

Species Election

Applicants respectfully affirm the provisional election made by telephone to prosecute the invention wherein the functional compound includes tetracycline. Claim 65 contains the limitation that the functional compound includes tetracycline. Claims 28, 30-31, 33-35, 37-38, 40, 42-44, 46, and 62-64 are generic. Claims 66 and 67 have been withdrawn as being drawn to a non-elected invention, there being no allowable generic claim.

Claim Rejections – 35 U.S.C. § 112

In the Office Action, claims 62 and 63 were rejected under 35 U.S.C. § 112 as failing to comply with the written description requirement. Specifically, the Office Action

states that specification does not support wherein the pH altering material includes an acid or a base. As noted in the specification, "such triggering of the delivery system may be accomplished through . . . the intentional act of introducing chemistries such as pH altering materials to the delivery systems to trigger the release of functional compounds." Pg. 16, lines 4-11. To satisfy the written description requirement, the issue is whether the specification describes the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. Applicants respectfully submit that one of ordinary skill in the art would reasonably conclude that a pH altering material could be an acid or a base. One of ordinary skill in the art understands that a primary means of pH altering in chemistry is accomplished by the addition of an acid or a base. As such, Applicants respectfully request withdrawal of this rejection.

Claim Rejections – 35 U.S.C. § 103

In the Office Action, independent claim 28 was rejected under 35 U.S.C. § 103(a) as being unpatentable over International Publication No. WO 03/032959 to Bosch et al. in view U.S. Patent No. 5,597,575 to Breitbarth and "Fundamentals of Adsorption" to Ma et al., as evidenced by Daraio et al. As a preliminary matter, Applicants respectfully request that Daraio et al. be made of record and provided to Applicants in following communications from the Office.

Bosch et al. is directed to nanoparticulate compositions comprising inorganic cores. The inorganic cores may be coated with pharmaceutically active agents to produce stable dispersions. However, as properly noted in the Office Action, Bosch et al. fails to disclose or suggest release of a functional compound from the surface of the

nanoparticles upon exposure to a pH change. Nevertheless, the Office Action cites Breitbarth as obviating this limitation. Breitbarth is directed to compositions for stimulating hair growth. The compositions include a non-metallic carrier coated with vitamin D_3. The carrier can be macroparticulate silica particles having a mean particle diameter of >40 microns, microparticulate silica particles having a mean particle diameter between 3 and 10 microns, or alumina microparticles with an average particle size of about 7 microns.

As a preliminary matter, Applicants note that one of ordinary skill in the art would not seek to combine the references in the manner taught in the Office Action. One of ordinary skill in the art would not look to the hair growth teachings of Breitbarth that discloses silica carriers with a minimum size of 3 microns (which is approximately **six times** the size of Applicants' claimed maximum **nanoparticle** size) in order to construct Applicants' claimed invention. Additionally, Breitbarth discloses a desire for microparticles with a negative surface charge. See claims 1, 16, and col. 2, lines 36-39. In stark contrast, Applicants claim nanoparticles with a zeta potential of 20 millivolts or more. Thus, Breitbarth teaches away from the combination as proposed by the Office Action.

Nevertheless, even if combined in the manner suggested in the Office Action, none of the references disclose the use of a plurality of nanoparticles containing **silica coated with alumina**. Indeed, the Office Action acknowledges this deficiency as it attempts to obviate this limitation utilizing the teachings of U.S. Patent No. 6,548,264 to Tan et al. and combining with the aforementioned references in a separate rejection (discussed below).

However, in this rejection, the Office Action points to Examples 1-3 of Bosch et al. that discloses the use of Nalco alumina as a nanoparticulate particle utilized. Then, the Office Action cites Daraio et al. as evidence that Nalco 1056 is alumina coated silica nanoparticles. Without commenting on the validity of Nalco 1056 being silica coated with alumina (as noted above, Applicants respectfully request this reference be made of record and provided in the following communication from the Office), Applicants note that Bosch et al. does **not** disclose the use of Nalco 1056 nanoparticles. Bosch et al. merely discloses the use of Nalco alumina. Indeed, Bosch et al. indicates the Nalco alumina products utilized in the examples comprise an alumina core (and not silica coated with alumina):

> The electron micrograph of Fig. 5 illustrates the Nalco alumina cores and the same material coated with naproxen. Pg. 27, lines 28-29.
> . . .
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> Figure 11 shows the ζ-potentials of both alumina cores, Nalco alumina (O) and Degussa C alumina (□), in $1x10^{-3}$ mol dm^{-3} aqueous NaCl solution . . . Pg. 34, lines 9-10.
> . . .
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> Figure 12 shows the ζ-potentials of both alumina cores, Nalco alumina (O) and Degussa C alumina (□), in $1x10^{-3}$ mol dm^{-3} aqueous NaCl solution . . . Pg. 34, lines 14-15.
> . . .
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> Figure 16 shows transmission electron micrographs of the Nalco alumina core (a) and of Nalco alumina core coated with naproxen (b). Pg. 35, lines 19-20.

Thus, clearly, the Nalco alumina of Bosch et al. does not anticipate Applicants' claimed nanoparticles containing silica coated with alumina. Furthermore, Applicants respectfully submit that it is improper to look to a company (Nalco) and cite a wholly different product (Nalco 1056) than disclosed in the reference ("Nalco alumina") as

evidence that the reference discloses Applicants' claimed subject matter when the complete disclosure of the reference indicates otherwise.

Additionally, the Office Action cites Ma et al. as obviating Applicants' claimed limitation of releasing tetracycline (claim 65) from the surface of nanoparticles upon exposure to a change in pH. Applicants respectfully note, however, that Ma et al. is directed to adsorption of proteins and antibiotics on alumina membranes during filtration. Ma et al. simply indicates that the amount adsorbed is dependent upon pH. However, in stark contrast, Applicants claim a functional compound bonded to the surfaces of nanoparticles and the release of the functional compounds from the surface upon exposure to a pH change. The teachings of Ma et al. alone, however, would in no way lead one of ordinary skill in the art to the modification suggested in the Office Action.

Additionally, even **if** the references were combined in the manner indicated in the Office Action, Applicants respectfully submit that the resulting combination still fails to obviate all of Applicants' limitations claimed in independent claim 28. Applicants claim "wherein the nanoparticles are contained within a vehicle that further comprises a pH altering material." As noted in the specification, such pH altering materials incorporated into the delivery system assists in triggering the release of the functional compounds. None of the references disclose or suggest such a component. Additionally, the Office Action fails to address the limitation.

Furthermore, the Office Action included a second rejection of all pending claims under 35 U.S.C. § 103(a) as being unpatentable over Bosch et al. in view Breitbarth and Ma et al., as evidenced by Daraio et al. (pg. 10 of the Office Action). However, the

rejection appears to be a replica of the first rejection addressed above with no new comments.

In the Office Action, independent claim 28 was also rejected under 35 U.S.C. § 103(a) as being unpatentable over Tan et al. in view of Bosch et al. and Breitbarth and Ma et al. as evidenced by Dario et al. Tan et al. describes core-shell nanoparticles in which the core may be a magnetic material (e.g., magnetite), metal or metal salt (e.g., gold), and so forth, and the shell may be silica or alumina. While Tan et al. may generally described alumina- or silica-coated nanoparticles, however, it does not disclose or suggest the claimed alumina-coated *silica nanoparticles*.

In order to yield this limitation, the Office Action points to an excerpt of Tan et al. that states that the shell can include a first layer of silica coating immediately adjacent to the core and a second layer coating the silica layer. The Office Action states "it would have been *prima facie* obvious for one skilled in the art . . . to make the nanoparticles of Tan et al. . . . wherein the shell comprises silica coated with alumina, as reasonably taught by Tan et al." Applicants respectfully disagree. The only mention of a second layer in Tan et al. discloses that

> the second layer can be composed of a biodegradable material (e.g., a sugar or polymer) impregnated with a drug. When introduced to an animal, the biodegradable material and drug will gradually be dissolved into the animal. Col. 6, lines 4-8.

Thus, Tan et al. does not reasonably teach silica coated with alumina. Furthermore, Tan et al. discloses that the shell may be composed of alumina or silica (among other potential components). Tan et al. does not motivate one skilled in the art to coat alumina onto silica nanoparticles.

In addition, the Office Action makes similar arguments with respect to Bosch et al. and Breitbarth and Ma et al. as evidenced by Dario et al. in this combination with Tan et al. Applicants restate their objections to these arguments as noted above.

Finally, Applicants emphasize that none of the cited references recognize the benefits achieved according to the present claims. Namely, the functionalized nanoparticles of the present claims may retain a positive surface charge, which can provide a variety of benefits. For example, the nanoparticles may better adhere to substrates that carry a negative surface charge *via* coulombic attraction. Consequently, a functional compound may be affixed to the substrate without the use of chemical binders or other attachment structures. Further, the nanoparticles may also better adhere to skin, mucosal membranes, etc. due to their high zeta potential. Thus, for at least the reasons set forth above, Applicants respectfully submit that the present claims patentably define over the cited references, taken singularly or in any proper combination.

It is believed that the present application is in complete condition for allowance and favorable action, therefore, is respectfully requested. Examiner Schlientz is invited and encouraged to telephone the undersigned, however, should any issues remain after consideration of this Response.

Please charge any additional fees required by this Response to Deposit Account No. 04-1403.

Respectfully requested,

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Date: December 5, 2008